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Lung function trajectories from pre-school age to adulthood and their associations with early life factors: a retrospective analysis of three population-based birth cohort studies

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ABSTRACT

Background: Maximal lung function in early adulthood is an important determinant of mortality and COPD. We investigated whether there are distinct trajectories of lung function during childhood, and whether these extend to adulthood and infancy.

Methods: To ascertain trajectories of forced expiratory volume in 1 second (FEV_1), we studied two population-based birth cohorts with repeat spirometry from childhood into early adulthood (1046 and 1390 participants). To ascertain whether trajectories extend to early life, we used a third cohort with repeat lung function measures in infancy (V'_{maxFRC}) and childhood (FEV_1 ; $n=196$). We identified trajectories using latent profile modelling. We created an allele score to investigate genetic associations of trajectories, and constructed a multivariable model to identify their early-life predictors.

Results: We identified four childhood FEV_1 trajectories: Persistently High; Normal; Below Average; and Persistently Low. Persistently Low trajectory (~5% of participants) was associated with persistent wheezing and asthma throughout follow-up. In genetic analysis, compared with the Normal trajectory, the pooled relative risk ratio (95%CI) per allele was: 0.96 (0.92, 1.01), $P=0.10$, for Persistently High; 1.01 (0.99, 1.03), $P=0.49$ for Below Average; and 1.05 (1.003, 1.09), $P=0.036$ for Persistently Low. The majority of children in low V'_{maxFRC} trajectory in infancy (~75%) did not progress to low FEV_1 trajectory in childhood. Early-life factors associated with Persistently Low trajectory included recurrent wheeze with severe exacerbations, early allergic sensitization, and tobacco smoke exposure.

Conclusion: Reducing childhood smoke exposure and minimising the risk of early-life sensitization and wheezing exacerbations may reduce the risk of diminished lung function in early adulthood.

Research in context

Evidence before this study

Early life factors, such as weight at birth, are associated with low lung function and chronic obstructive pulmonary disease (COPD) in late adulthood. Lung function development reaches a plateau in early adult life, and low lung function in young adults is associated with early mortality from all causes. Failure to attain maximal lung function at its plateau is associated with COPD in later life, even when with physiological rate of decline of lung function is maintained. This strengthens the evidence that early life influences may be critical for normal lung function growth in childhood and COPD pathogenesis.

Added value of this study

Using data from population-based, birth cohort studies, we demonstrated four discrete trajectories of FEV₁ development from early childhood to young adulthood. Persistently low FEV₁ was associated with wheezing and asthma through childhood, tobacco smoke exposure and was predicted by severe recurrent wheezing and allergic sensitization by age 3 years. We were able to determine from a third independent cohort that the majority of infants with low infant lung function trajectory during the first year after birth transitioned to normal or above average FEV₁ trajectories

Implications of all the available evidence

A persistently low trajectory of FEV₁ development can be identified during childhood, which is associated with potentially modifiable influences in early childhood. This trajectory was replicated in a companion study that followed FEV₁ growth from childhood to late adulthood. Although perinatal factors are associated with low lung function during childhood and with later COPD, the majority of infants with low lung function trajectories during the first year appeared to recover to average or above average FEV₁ growth in later childhood. Interventions to maximise lung growth in early childhood may modify the risk of COPD in older age.

INTRODUCTION

Low forced expiratory volume in 1 second (FEV₁) in early adult age (at its physiological plateau) is as important in the genesis of chronic obstructive pulmonary disease (COPD) as a rapid decline of FEV₁ in later years.¹⁻³ Furthermore, low lung function in young adult life is associated with early mortality,⁴ and low FEV₁ is a marker of premature death from all causes.⁵ A recent study by Agustí *et al* has shown that low lung function in early adulthood (around the time of the physiological plateau) is associated with earlier onset of COPD, other chronic diseases, and death.⁶ An accompanying Editorial highlighted the need to use longitudinal studies and modern statistical approaches to gain better understanding of the causal pathways, understand the critical windows for lung function development, and identify targets for early intervention.^{4,5,7-11}

Hypothesis-driven analyses in unselected longitudinal cohorts and children with asthma have shown that lung function in adult life is in part determined by childhood events. The observation that FEV₁ was consistently lower amongst individuals with certain clinical phenotypes (such as severe asthma,⁸ and persistent wheezing⁹) provided foundations for the concept that lung function tracks from school-age to adulthood.^{9,10} This is supported by the data-driven analysis of spirometry records from childhood (age 11 years) to the fourth decade of life in Tucson cohort, which identified two distinct lung function trajectories (low and normal).¹¹ Persistently low trajectory comprised nearly 10% participants, and individuals in this class were predisposed to COPD later in life.

We hypothesized that a population comprises several distinct groups of individuals with similar lung function trajectories from pre-school age to adolescence, which extend to the physiological plateau in early adulthood, and that these trajectories are in part established at birth. However, factors which

determine lung function growth may differ from those affecting the rate of decline after the plateau,¹² and inference from models that combine a limited number of measures in childhood (before peak lung function is reached in early adulthood), with those in later adulthood (during the decline phase), may not adequately disaggregate the effects of risk factors which differentially impact growth and decline. To address our hypotheses, and ascertain trajectories during the lung function growth and their risk factors, we combined data from three population-based birth cohorts in which lung function was assessed on multiple occasions from infancy, through early school age and adolescence, into early adulthood. We first set out to establish whether a method to categorise FEV₁ trajectories using latent profile analysis could be applied across different cohorts, and whether it yields consistent results across different populations. We proceeded to identify genetic and early-life factors associated with FEV₁ trajectories at the population level. Finally, we investigated whether FEV₁ trajectories track back to lung function patterns in infancy.

METHODS

Study design, setting and participants

We studied three population-based birth cohorts: Manchester Asthma and Allergy Study (MAAS)¹³ and the Avon Longitudinal Study of Parents and Children (ALSPAC)¹⁴ from the UK STELAR consortium¹⁵, and the Australian Perth Infant Asthma Follow-up (PIAF) study.¹⁶ All participants were recruited prenatally, and followed prospectively. All studies were approved by research ethics committees. Informed consent was obtained from parents, and study subjects gave their consent when applicable.

Data sources/measurement

We investigated trajectories of FEV₁ from early school-age to adolescence in MAAS¹³ and replicated these using data from ALSPAC from school age to early adulthood¹⁴. We ascertained whether FEV₁ trajectories extended to lung function in early infancy using data from PIAF.¹⁷

We performed spirometry according to ATS/ERS criteria^{18,19} at ages 5, 8, 11 and 16 years in MAAS; ages 8, 15 and 24 years in ALSPAC; and 6, 12 and 18 years in PIAF. We expressed FEV₁ as % predicted at each age.²⁰ In PIAF, we assessed infant lung function at ages 1, 6 and 12 months using the rapid thoracoabdominal compression test to determine the maximal flow at functional residual capacity (V'_{maxFRC}).^{16,17} In MAAS we measured specific airways resistance (sR_{aw}) at age 3 years.²¹ In MAAS and ALSPAC, we measured post-bronchodilator FEV₁ after administration of 400 µg of salbutamol (5, 11 and 16 years in MAAS, and 15 and 24 years in ALSPAC), and assessed airway hyper-reactivity (AHR) using methacholine challenge.²²

Details of clinical follow up, genotyping (MAAS and ALSPAC), and definitions of clinical outcomes (asthma,²³ wheeze phenotypes,²⁴ severe asthma exacerbations,²⁵ airway hyper-reactivity (AHR),²⁶ lower

respiratory tract infections [LRTIs]²⁷), and environmental exposures are presented in the supplementary appendix.

Statistical Analysis

Longitudinal profile analysis to assess prototypical FEV₁ trajectories: We used a latent profile model to assign children to their most likely group based on the profile of FEV₁ over time. Latent profile modelling has been described extensively elsewhere.²⁸ Briefly, we assumed that each child belonged to one of a set of N latent profiles, the number or size of which were unknown *a priori*. We used two-level random intercept and random coefficients regression models to examine trajectory classes with no change over time, and under the assumption that the profile of FEV₁ changes linearly over time. The models were compared for goodness-of-fit using the Bayesian Information Criterion (BIC). For each child, the posterior probability of belonging to each of the classes was calculated, and children were assigned to the latent profile with the largest probability. Latent profile modelling was carried out using the gllamm (generalised linear latent and mixed models) package implemented in Stata (StataCorp, College Station, TX). Characteristics of trajectories were investigated using multinomial regression.

Genetic associations with FEV₁ trajectories: We constructed a weighted allele score from 77 SNPs found to have genome-wide evidence for association with FEV₁/FVC, or FEV₁ decline in adults²⁹ (Table S1, supplementary appendix). The dosage of the risk allele at each locus was multiplied by a SNP-specific weight (linear coefficient [beta] divided by the average of 77 linear coefficients), then averaged across SNPs. SNP-specific risk alleles and weights were based on the reported meta-analysis.²⁹ The units of the derived genetic score were per-beta per-SNP. Setting the 'Normal' trajectory as the baseline group, we used a multinomial logistic regression model to investigate the risk of the membership of other trajectories per 1-unit increase of the genetic score. The independent associations of the resulting genetic risk score with FEV₁ trajectories in MAAS and ALSPAC were meta-analysed with fixed and

random effect models using the method of Mantel and Haenszel (*metan* command in Stata). Using multinomial logistic regression models, we also calculated the relative risk ratios for ‘Persistently Low’ (vs. ‘Normal’ trajectory) in extreme quantiles of the allelic risk score in two cohorts independently (deciles in ALSPAC; eight quantiles in MAAS).

Identification of the early-life predictors of FEV₁ trajectories: We constructed a multivariable regression model to identify early-life predictors of subsequent latent profiles of FEV₁. We carried out these analyses in MAAS, in which we had richer data collected in early life. We used receiver operating characteristic (ROC) curves to evaluate the predictive ability of these predictors.

Role of the funding source

The study sponsors had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

RESULTS

We included 1046 participants from MAAS, 1390 from ALSPAC, and 196 from PIAF. Participant flow is presented in the Supplementary appendix.

FEV₁ trajectories from early school-age to young adulthood (MAAS and ALSPAC)

We selected 4-class model in MAAS and ALSPAC (please see Supplementary appendix and Table S2).

The posterior probability of class membership was high in both cohorts (Table S3). The proportion of participants and the mean FEV₁ over time in each of the classes were similar across the cohorts (Table S4). We labelled the classes (FEV₁ trajectories) as: (1) Persistently High; (2) Normal; (3) Below Average; and (4) Persistently Low (Figure 1). Children within these four trajectories had stable lung function that tracked from age 5 to age 16 years (MAAS), and from ages 8 to 24 years (ALSPAC), with no overlap in FEV₁ at any time. The solutions remained stable and results unchanged when we included only children who had spirometry on at least 3 follow-ups (Tables S5-6).

Characteristics of children in each of the FEV₁ trajectories are shown in Tables S7 and S8. Persistently Low trajectory was consistently associated with wheeze and asthma throughout the follow-up in both cohorts; in MAAS, almost half the children in this trajectory had asthma, and in ALSPAC this was approximately one third, significantly higher than in the rest of the population. The proportion of children with LRTIs in the first 3 years (data from medical records, available only in MAAS²⁷) was significantly higher in the Persistently Low trajectory (32.3%) compared to the Normal trajectory (12.1%). Post-bronchodilator FEV₁ and FEV₁/FVC followed similar patterns as the baseline FEV₁ in both cohorts. In MAAS, sR_{aw} at age 3 years was significantly higher in Persistently Low compared to other trajectories, indicating diminished lung function (P=0.001). Persistently Low trajectory was significantly associated with AHR in both cohorts. There was no association between trajectory membership and

allergic sensitisation in adolescence in MAAS, or at age 7 years in ALSPAC. Sensitisation in early childhood in MAAS was significantly more common in Persistently Low trajectory.

There was no difference in gender between trajectories. Birth weight was significantly higher in the Persistently High trajectory in ALSPAC, but not in MAAS. In MAAS, children in the Persistently High trajectory were less likely to be exposed to environmental tobacco smoke (ETS) compared to all others (Figure 2a). Children continuously exposed to ETS from birth to age 16 years were at increased risk of belonging to the Below Average and Persistently Low trajectories. We observed similar trends in ALSPAC, with Persistently High trajectory having the lowest proportion of ETS-exposed participants (Figure 2b).

Genetic associations

Genotyping data was available in 927 participants in ALSPAC, and 902 in MAAS. The weighted genetic score based on 77 SNPs was inversely associated with the order of FEV₁ trajectories (Persistently High to Persistently Low) in both cohorts (Table S9). The meta-analysis is shown in Figure 3: compared with the Normal trajectory, the pooled relative risk ratio (95%CI) per allele was: 0.97 (0.92, 1.01), P=0.13, for Persistently High; 1.01 (1.00, 1.03), P=0.49 for Below Average; and 1.05 (1.00, 1.09), P=0.036 for Persistently Low. Results using the inverse variance method were very similar. Risk of Persistently Low FEV₁ (vs. Normal) in 10th decile of risk score (vs. 1st decile) was 2.03 (0.62, 6.67), p=0.24 in ALSPAC. In MAAS, the risk of Persistently Low FEV₁ in the highest compared with the lowest of eight quantiles was 4.19 (0.83-21.05), p=0.08.

Do FEV₁ trajectories extend back to lung function in early life (PIAF)?

In PIAF, a 3-class model provided the optimal solution for FEV₁ (Above Average, Normal and Below Average, Figure 4a), and a 2-class model for V'_{maxFRC} (Above Average and Below Average, Figure 4b).

Among children in the Below Average FEV₁ trajectory, $V'_{\max\text{FRC}}$ was significantly lower compared to other trajectories at age 1 month (P=0.05) and 6 months (P=0.018), but not at age 1 year (Table S10). Although children in the Below Average $V'_{\max\text{FRC}}$ trajectory were significantly more likely to remain in the Below Average FEV₁ trajectory (OR=3.63, 95%CI 1.21–10.90, P=0.022), the majority of these children (~75%) transitioned to the Above Average (12.2%) or Normal (63.4%) FEV₁ trajectories in later childhood (Figure 4, panel c).

Early-life predictors of FEV₁ trajectories (MAAS)

Children with recurrent severe wheeze exacerbations by age 3 years, with allergic sensitization at age 3 years, and who have been exposed to ETS by age 3 years, were more likely to belong to the Persistently Low trajectory (Table S10). This set of variables provided a good predictive ability in MAAS for discriminating between subjects in Persistently Low from Persistently High trajectory (Figure 5, Area Under the ROC Curve-AUROC=90.7%, sensitivity=81.8%; specificity=80.95%), and a fair predictive ability for discriminating between subjects in Persistently Low from all others (Figure S1, AUROC=77.2%, sensitivity=81.8%; specificity=67.8%).

We found an association between low birth weight and low childhood FEV₁ trajectories. In MAAS, which included no preterm infants, low birth weight (LBW) at term (<2500g) was associated with Persistently Low FEV₁ (Odds ratio 3.39 [95% CI 0.98-11.77], p=0.055). In ALSPAC, LBW adjusted for preterm (<37 weeks) gestation at birth was associated with Persistently Low FEV₁ (OR 1.98 [0.65-5.99], p=0.226, and Below Average FEV₁ (OR 1.84 [0.91-3.73], p=0.09).

DISCUSSION

In two population-based birth cohorts, using data-driven analyses we identified four distinct lung function trajectories extending from early school age, through mid-school age, into adolescence and early adulthood. Subjects assigned to the Persistently Low trajectory, representing approximately 1 in 20 participants, had low lung function in the third decade of life, around the time of the physiological plateau. Individuals in this trajectory had FEV₁ below 80% predicted from early childhood to the point beyond which lung function starts to decline with aging.^{3,20} In the Persistently Low trajectory, both baseline and post-bronchodilator FEV₁ was up to 25% lower, and FEV₁/FVC up to 10% lower than the next lowest category. This tracking of lung function from early school-age is consistent with previous reports from population-based studies^{9,10}, and provides confirmatory empirical evidence of this phenomenon based on a hypothesis-free approach. In addition to using data-driven analyses, another novel feature of the present study was the extension of lung function trajectories to early childhood, where spirometry is not practicable, and the observation that “low” lung function recovered in the majority of cases. At group level, children in the Low FEV₁ trajectory in PIAF had significantly diminished lung function in infancy (measured by V'_{maxFRC}), which is very similar to the finding in MAAS that, as a group, those in Persistently Low FEV₁ trajectory had significantly diminished lung function at age 3 years (measured by sR_{aw}). However, comparison of lung function trajectories in infancy and in school-age in PIAF has shown that although infants in the Below Average V'_{maxFRC} trajectory were significantly more likely than children in the higher V'_{maxFRC} categories to be classified in the Below Average FEV₁ trajectory in childhood, the majority of these children (~75%) transitioned to the Above Average (12.2%) or Normal (63.4%) FEV₁ trajectories. These findings are consistent with previous results from PIAF obtained using standard hypothesis-testing analyses,^{17,30} and support the concept of postnatal “recovery” of low neonatal lung function. The application of the same data-driven approach to longitudinal analysis as used in the MAAS, ALSPAC and Tasmanian Longitudinal Health Study (TAHS),³¹ allows some inference to

the general population on the patterns of lung function from one month of age to the sixth decade. Disaggregation of this population into discrete trajectories suggests that the opportunity for lung function recovery extends beyond the neonatal period.

Our data revealed no evidence of groups of children with declining FEV₁. A report from TAHS published in this issue of the journal, which used a similar statistical approach to discovery of lung function trajectories and spanned childhood (7-18 years) and later adulthood (45-55 years), described six trajectories, four of which were strikingly similar to ours.³¹ One further trajectory with below average FEV₁ by age 18, and accelerated decline in later adulthood after reaching the plateau, could not be captured within our data set. This trajectory was characterized by both childhood factors and personal smoking in adulthood, which were independent risk factors. Together, our studies and TAHS elucidate the developmental patterns of lung function through the life-course, confirm their link with COPD, and provide evidence that different factors affect lung function growth from those affecting lung function decline. We have shown that Persistently Low trajectory is determined by both genetic factors and early-life events. We showed relatively weak evidence that SNPs discovered through GWAS of adult lung function²⁹ were associated with a low childhood trajectory of FEV₁. This suggests an influence of at least some of the included variants on lung function in early life but, as they were derived from studies of adults, it is likely that they consisted of a combination of factors influencing lung function growth and decline. A recent study of adults with repeat lung function measures showed that genetic variants associated with cross-sectional lung function in adults were not associated with longitudinal decline, suggesting that some of the observed association may be explained by developmental influences³². We did not have sufficient statistical power in this sample to investigate the individual contributions of risk alleles nor to construct a *de novo* GWAS.

Individuals with Persistently Low FEV₁ in childhood have low maximally attained lung function in early adulthood, and are consequently at higher risk of COPD³¹, with or without additional adverse exposures in adulthood. Personal smoking acts as an independent risk factor which contributes to accelerated lung function decline in middle adulthood, predominantly among individuals with below average lung function.³¹ In this group, in addition to early-life risk factors contributing to the diminished lung function at physiological plateau, adverse exposures in adult life lead to COPD development. Childhood asthma and early-life LRTIs are associated with low lung function trajectories and higher COPD risk in both scenarios. We found an association between asthma reported at all available ages and persistently Low FEV₁ trajectory. This is consistent with previously reported associations between persistent asthma in childhood and subsequent lung function^{8,9} but we acknowledge the potential for misclassification of symptoms associated with pre-existing airway obstruction and asthma diagnosis, particularly when relying on self-report from questionnaires for the latter. This limits interpretation of the causal pathway between asthma in childhood

Although children with severe wheeze and early sensitization had lower FEV₁ throughout childhood, their FEV₁ remained relatively stable. In contrast, a recent study of FEV₁ trajectories between ages 7 and 26 years among patients with childhood asthma described two trajectories characterized by decline (Normal growth and early decline, and Reduced growth with early decline).³³ However, direct comparison with our findings is not possible, as our cohorts are population-based, and we used data-driven approach rather than predetermined categorization to identify trajectories. In MAAS, similar proportions of children (approximately one third) in Persistently Low trajectory had persistent wheeze and transient early wheeze, whilst <10% had late-onset wheezing. This is in contrast with the Australian

high-risk cohort, which suggested that only persistent wheeze is associated with reduced growth in FEV₁ over adolescence, but that transient wheeze is a benign condition with no sequelae.³⁴ In MAAS, an important predictor of subsequent Persistently Low FEV₁ trajectory was severe exacerbation of wheezing in early life, rather than only wheezing persistence. Low birth weight, which is associated with tobacco some exposure during pregnancy and early onset wheezing in infancy was associated with low childhood FEV₁ trajectories in our study independently of preterm delivery. This may be explained by restricted intrauterine growth influencing airway development and subsequent lung function³⁵ with an associated tendency to wheezing in the context of LRTIs.

Persistently Low lung function trajectory was also identified in the Tucson cohort (comprising nearly 10% participants),¹¹ and is remarkably similar to our Persistently Low trajectory, which comprised a sizeable proportion (3.4%-6.7%) of our study populations. Assuming that 13.3% of the population develop COPD (<http://www.hse.gov.uk/Statistics/causdis/copd/copd.pdf>), and that among these, subjects in the Persistently Low trajectory would likely be diagnosed with COPD,³⁴ the calculated population attributable risk is 22.9%-46.7%. This also represents the estimated reduction in COPD which would occur if early interventions improve lung function for this group. To inform potential strategies for improving lung function in early adulthood, we have identified early-life risk factors associated with Persistently Low trajectory, which in addition to genetic factors included early-life ETS exposure, recurrent severe exacerbations of wheezing, and early allergic sensitisation. A recent study suggested that adult smoking, but not parental smoking history, can negatively influence adult lung function trajectory and modify the adverse impact of early-life exposures.³⁵ Our and TAHS data demonstrate that both are important. We identified an association between the absence of early-life tobacco smoke exposure and Persistently High trajectory, which In TAHS had markedly lower risk of COPD at age 55 years.³¹ Thus, while tobacco smoke exposure will not necessarily lead to a disease, the absence of this

exposure is associated with exceptionally good lung function and subsequent health. The risk of being in one of the diminished lung function profiles was decreased by 76% among children who were not exposed to parental smoking, suggesting that ETS exposure in early childhood may be causally related to COPD development, and that this may be mediated via the effect of early-life exposure on subsequent trajectories of lung function into adulthood.

Strengths and limitations

One of the limitations of our study is that it was not possible to have identical measures of lung function through the life-course in our cohorts. We did not measure spirometry before age five years, since forced expiratory manoeuvres are difficult to carry out in young children. We used different cohorts and age-appropriate measures of pulmonary function to make inference about the life-course (rapid thoraco-abdominal compression in infancy¹⁶, plethysmography in pre-school age³⁶, spirometry from school age onwards), which may represent the best available approximation of what might be happening from birth to adulthood. Another limitation is that the questions we used contained small differences in wording.³⁷ ALSPAC included pre-term babies, which may explain slightly higher proportion of children in the Persistently Low trajectory in ALSPAC (6.7%, compared to 3.4% in MAAS), and the finding in ALSPAC that birth weight was significantly lower in trajectories with diminished lung function. One of the strengths of this study is the ability to disambiguate the temporal structure of profiles during childhood, allowing us to identify patterns during the lung function growth phase. It is striking that although we modelled data collected at different time points, and separately for each cohort, the results indicated almost identical latent profiles. In PIAF, we did not observe Persistently Low FEV₁ trajectory. This is not surprising, given a relatively small proportion of children in this trajectory (~5%), and a considerably smaller size of PIAF compared to MAAS and ALSPAC.

We are also cognizant of the potential effect of the withdrawal/missing data rates. We carried out our analyses under the assumption that data was missing at random. To test this assumption, we carried out analyses using both children with at least three data points available, and those with at least one time point. Both analyses gave consistent optimal goodness-of-fit using the BIC, and the child class assignments were stable across the two analyses. This suggests that the missing at random assumption was plausible, given that if children with missing data points were not missing completely at random, there would have been a higher mismatch between classes.

Conclusion

Using data from population-based birth cohort studies, we demonstrated four discrete trajectories of FEV₁ development from early childhood to young adulthood. Interventions to reduce the risk of Persistently Low FEV₁ trajectory should start in early childhood, and should include aggressive strategies to reduce tobacco smoke exposure, and novel strategies to prevent early-life sensitization and exacerbations of early-childhood wheezing.

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Authors' contributions: AC, AJH and AS conceived the idea; DB, RG and IEB provided input on the methodology for analyzing the data; DB, RG and JAC carried out the analyses; AC, AJH, DB, SWT, PNLS and AS interpreted the data; all authors wrote the report. The corresponding author (AJH) had access to all the data in the study and takes final responsibility for the decision to submit for publication.

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LEGENDs FOR FIGURES

Figure 1: Mean % Predicted FEV₁ over time by FEV₁ trajectory:

- a) MAAS
- b) ALSPAC

Figure 2: % Children exposed to Environmental Tobacco Smoke over time by FEV₁ trajectory:

- a) MAAS
- b) ALSPAC

Figure 3: Meta-analysis (random effects model) of weighted genetic score based on 77 SNPs with FEV₁ trajectories

Figure 4: Lung function trajectories in PIAF:

- a) Mean % Predicted FEV₁ over time by FEV₁ trajectory
- b) Mean % Predicted V'_{maxFRC} over time by V'_{maxFRC} trajectory
- c) Membership of FEV₁ trajectory in relation to the V'_{maxFRC} trajectories

Figure 5: Receiver Operating Characteristic Curve showing predictive ability of a logistic regression analysis using the Persistently Low vs. Persistently High trajectory as the outcome (or predicted) measure with the following covariates: (1) recurrent wheeze with severe exacerbations by age 3 years, (2) at least one positive skin test by age 3 years, and (3) Environmental Tobacco Smoke exposure by age 3 years